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(54) Title: STEROL ESTERS AS FOOD ADDITIVES (57) Abstract A food additive useful for lowering serum cholesterol in humans contains a sterol or stanol ester of a fatty acid or a dicarboxylic acid ester of a sterol or stanol made by reacting a sterol, stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof described herein.		

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STEROL ESTERS AS FOOD ADDITIVES

BACKGROUND OF THE INVENTION:

5 Phytosterols have been found to be effective in reducing serum cholesterol in humans. Phytosterols are steroids that bear a close structural relationship to cholesterol but differ in the configuration of the side chains at the 17-position. It is well known that β -sitosterol and the fatty acid esters of β -sitosterol are effective in reducing serum cholesterol. Recent studies have
10 found that β -sitostanol and the fatty acid esters of β -sitostanol are particularly effective in reducing serum cholesterol and LDL levels. It has been recently reported that the fatty acid esters of β -sitostanol are particularly effective cholesterol-reducing agents presumably because they are in solution. Such esters can be introduced into the body as additives in food products such as
15 margarine. Margarines containing β -sitosterol and those containing β -sitosterol fatty acid esters as well as margarines containing β -sitostanol and β -sitostanol fatty acid esters have been shown to reduce serum cholesterol levels in humans.

BRIEF SUMMARY OF THE INVENTION:

20 The present invention pertains to a food additive containing a sterol or stanol ester of a fatty acid or a dicarboxylic acid ester of a sterol or stanol made by the process described herein below. The food additive can be incorporated into food for the purpose of lowering serum cholesterol in humans and/or for reducing the absorption of cholesterol from foods and/or
25 beverages. The food additive is prepared by combining a sterol and/or stanol fatty acid ester thereof and/or a dicarboxylic acid ester of a sterol or stanol made by the process described herein and an edible solubilizing agent, an effective amount of a suitable antioxidant and an effective amount of a suitable dispersant. The sterol and/or stanol esters made by the process

described herein can be used without removing the catalyst because the catalyst is non-toxic and used at low levels. Another advantage is that when the fatty acid esters of sterols or stanols are prepared by transesterification, the ester that is transesterified can be either a lower alkyl ester such as a methyl or an ethyl ester or a triglyceride which is a triglyceryl ester of a C₆₋₂₂ fatty acid such as a conventional fat or oil.

Another aspect of the invention pertains to a method of reducing the absorption of cholesterol into the bloodstream which comprises orally introducing into the body an effective amount of a substance containing a β -sitostanol ester made by reacting a stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING:

Not Applicable.

DETAILED DESCRIPTION OF THE INVENTION:

The term sterol is well known to those skilled in the art and generally refers to those compounds having a perhydrocyclopentanophenanthrene ring system (the ring system depicted in Formula III herein) and having one or more OH substituents, examples of which include, but are not limited to, cholesterol, campesterol, ergosterol, sitosterol, and the like. It is common to obtain sterols as mixtures of compounds such as, for example, GENEROL® 122N sterols, a trademark product of Henkel Corporation, Gulph Mills, PA. GENEROL® 122N sterol contains 25-30% campesterol, 17-22% stigmasterol and 45-50% sitosterol.

The term stanol is well known to those skilled in the art and generally refers to those compounds having a saturated perhydrocyclopentanophenanthrene ring system (the ring system depicted in Formula II herein) and having one or more OH substituents, examples of which include, but are not limited to, campestanol, sitostanol which also

known as β -sitostanol and stigmastanol, coprostanol, cholestanol and the like.

The food additive according to the invention is comprised of a sterol and/or stanol ester of a fatty acid wherein the ester is made by reacting a sterol and/or stanol with a fatty acid having from 6 to 22 carbon atoms in the presence of an effective amount of a catalyst selected from the group

consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof or a dicarboxylic acid ester of a sterol or stanol of the formula I. Since the catalyst is non-toxic and

used at low levels, the sterol and/or stanol ester of the fatty acid can be

added directly to foods without further processing such as removal of the catalyst. The sterol can be any sterol. Examples of suitable sterols include, but are not limited to, campesterol, ergosterol, stigmasterol, sitosterol or a combination thereof. A preferred sterol is β -sitosterol. A commercially available combination of sterols is GENEROL® 122N sterols as set forth

herein. The stanol can be any stanol. Examples of suitable stanols include, but are not limited to, campestanol, sitostanol which is also known as β -sitostanol and stigmastanol, coprostanol, cholestanol and the like. A preferred stanol is β -sitostanol.

The amount of sterol and/or stanol fatty acid ester that can be used in the food additive is an effective amount which is any amount necessary to either reduce serum cholesterol in humans after ingestion of a food containing the food additive or an amount necessary to reduce the absorption of cholesterol from foods and/or beverages. A preferred food additive composition of the instant invention comprises from about 70% to about 80% vegetable oil, from about 1% to about 2% tocopherols, and from about 10% to about 25% sterol and/or stanol fatty acid ester prepared by the method according to the invention.

The food additive is prepared by combining a sterol and/or stanol ester of a fatty acid made by the process described herein and an edible solubilizing agent, an effective amount of a suitable antioxidant and an effective amount of a suitable dispersant. The solubilizing agent can be vegetable oil such as, for example, sunflower oil, palm kernel oil, coconut oil,

rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame oil, safflower oil, and the like, monoglycerides, diglycerides, triglycerides, tocopherols, and the like, and mixtures thereof. The antioxidant can be ascorbic acid (Vitamin C), tocopherols such as α -tocopherol (vitamin E), β -carotene, an extract of the bark of the maritime pine, *Pinus maritima* and combinations thereof. The extract of the bark of the maritime pine, also known as PYCNOGENOL™, contains procyanidines consisting of catechin and epicatechin units linked by C-C bonds to form dimers, trimers and other oligomers up to a chain length of 6-7 molecules and phenolic acids and its glucose derivatives. PYCNOGENOL™ is produced according to U.S. Pat. No. 4,698,360, which is incorporated herein for reference. The extract used according to the invention may be prepared essentially by extracting maritime pine bark in comminuted form with boiling water, saturating the filtered extract with sodium chloride or, alternatively, adding ammonium sulfate to 20% w/v, separating the precipitate formed, repeatedly extracting the supernatant with 1/10 volume of ethyl acetate, drying the collected ethyl acetate extracts, concentrating the dried extract, pouring it into 3 volumes of chloroform with stirring and collecting the precipitate which may be purified by repeating the dissolution in ethyl acetate and precipitation with chloroform. Mixtures of the above antioxidants can also be used.

A suitable dispersant is any biologically acceptable surface active agent, examples of which include, but are not limited to, an alkyl polyglycoside, lecithin, polysorbate 80, sodium lauryl sulfate, and the like. The alkyl polyglycosides which can be used in the invention have the formula V



wherein R_1 is a monovalent organic radical having from about 6 to about 30 carbon atoms; R_2 is a divalent alkylene radical having from 2 to 4 carbon atoms; Z is a saccharide residue having 5 or 6 carbon atoms; b is a number having a value from 0 to about 12; a is a number having a value from 1 to about 6. Preferred alkyl polyglycosides which can be used in the compositions according to the invention have the formula I wherein Z is a glucose residue and b is zero. Such alkyl polyglycosides are commercially

available, for example, as APG®, GLUCOPON®, PLANTAREN® or AGRIMUL® surfactants from Henkel Corporation, Ambler, PA, 19002.

Examples of such surfactants include but are not limited to:

- 5 1. GLUCOPON® 220 Surfactant - an alkyl polyglycoside in which the alkyl group contains 8 to 10 carbon atoms and having an average degree of polymerization of 1.5.
2. GLUCOPON® 225 Surfactant - an alkyl polyglycoside in which the alkyl group contains 8 to 10 carbon atoms and having an average degree of polymerization of 1.7.
- 10 3. GLUCOPON® 600 Surfactant - an alkyl polyglycoside in which the alkyl group contains 12 to 16 carbon atoms and having an average degree of polymerization of 1.4.
4. GLUCOPON® 625 Surfactant - an alkyl polyglycoside in which the alkyl group contains 12 to 16 carbon atoms and having an average degree of polymerization of 1.4.
- 15 5. APG® 325 Surfactant - an alkyl polyglycoside in which the alkyl group contains 9 to 11 carbon atoms and having an average degree of polymerization of 1.6.
6. PLANTAREN® 2000 Surfactant - an alkyl polyglycoside in which the alkyl group contains 8 to 16 carbon atoms and having an average degree of polymerization of 1.4.
- 20 7. PLANTAREN® 1300 Surfactant - an alkyl polyglycoside in which the alkyl group contains 12 to 16 carbon atoms and having an average degree of polymerization of 1.6.
- 25 8. AGRIMUL® PG 2067 Surfactant - an alkyl polyglycoside in which the alkyl group contains 8 to 10 carbon atoms and having an average degree of polymerization of 1.7.

Other examples include alkyl polyglycoside surfactant compositions which are comprised of mixtures of compounds of formula I as described in
30 U.S. patents 5,266,690 and 5,449,763, the entire contents of both of which are incorporated herein by reference.

The method by which the novel food additive composition is used to

reduce cholesterol absorption from foods and beverages includes the step of commingling the food additive composition with foods and beverages, mixing until uniformly blended. The novel food additive is effective as an additive in margarine, cooking oils or shortening for the purpose of reducing serum

5 cholesterol in humans who ingest food products made with the novel additive. Margarine containing the novel food additive can be made by methods well known to those skilled. A general method for making margarine is disclosed in pages 77-84 of Volume 3 of Bailey's Industrial Oil and Fat Products (1985), the entire contents of which are incorporated herein by reference. The

10 amount of sterol and/or stanol fatty acid ester useful in the novel food additive is an effective amount which is any amount necessary to either reduce serum cholesterol in humans after ingestion of a food containing the food additive or an amount necessary to reduce the absorption of cholesterol from foods and/or beverages. A preferred food additive composition of the instant

15 invention comprises from about 70% to about 80% vegetable oil, from about 1% to about 2% tocopherols, and from about 10% to about 25% sterol and/or stanol fatty acid ester prepared by the method according to the invention. Particularly preferred compositions are composed of from about 70% to about 80% sunflower oil and/or rape seed oil, from about 1% to about 2% vitamin E

20 and/or an extract of the bark of the maritime pine, *Pinus maritima* and from about 10% to about 25% of a sterol and/or stanol fatty acid ester prepared by the method according to the invention.

Another aspect of the invention pertains to a method of reducing the absorption of cholesterol into the bloodstream which comprises orally

25 introducing into the body an effective amount of a substance containing a β -sitostanol ester made by reacting β -sitostanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof. The cholesterol-

30 lowering ability of fatty acid esters of β -sitostanol is described in U.S. patent 5,502,045, the entire contents of which are incorporated herein by reference. The fatty acid esters of β -sitostanol made by the process described herein

can be orally introduced by ingesting food products containing the food additives of the present invention. Preferred methods of oral introduction of the β -sitostanol made by the process described herein is through the ingestion of margarine, cooking oils or shortening containing a food additive according to the invention. A particularly effective amount of β -sitostanol fatty acid esters is from about 0.2 to about 20 grams per day. Particularly preferred additives are composed of from about 70% to about 80% sunflower oil and/or rape seed oil, from about 1% to about 2% vitamin E and/or an extract of the bark of the maritime pine, *Pinus maritima* and from about 10% to about 25% of a β -sitostanol fatty acid ester prepared by the method according to the invention.

In regard to the esterification process used to make the sterol and/or stanol esters which can be used in the novel food additive, any aliphatic, cycloaliphatic, or aromatic mono- or poly-carboxylic acid having at least 2 carbon atoms or mixtures of such acids can be used in the process according to the invention. Examples of aliphatic mono-carboxylic acids include, but are not limited to acetic, propionic, valeric, pelargonic, palmitic, lauric, oleic, linoleic acid, and the like. Examples of cycloaliphatic mono-carboxylic acids include, but are not limited to cyclopentane carboxylic acid, cyclohexane carboxylic acid, cyclohexene carboxylic acid and the like. Examples of aromatic mono-carboxylic acids include, but are not limited to benzoic acid, toluic acid, aminobenzoic acid and the like. Examples of aliphatic poly-carboxylic acids include, but are not limited to oxalic, malonic, adipic, azelaic acid, C-36 dimer acid, citric acid and the like. Examples of aromatic poly-carboxylic acids include, but are not limited to phthalic acid, trimellitic acid and the like. Preferred carboxylic acids are mixtures of long chain carboxylic acids such as those derived from naturally occurring oils such as sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame oil, safflower oil, and the like which are known to those skilled in the art and are disclosed in chapter 6 of Volume 1 of the fourth edition (1979) of Bailey's Industrial Oil and Fat Products, the entire contents of which are incorporated herein by reference. Preferred fatty acid

mixtures are those obtained from sunflower oil and rape seed oil.

5 The direct or transesterification modifications of the esterification processes can be carried out in the presence of a calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide catalyst or a combination of such catalysts. One advantage of the method according to the invention is that the calcium or magnesium catalysts can be left in the product or removed by contacting the reaction product with a chelating agent such as L-tartaric acid or EDTA. The preferred catalysts are calcium hydroxide, calcium oxide and the calcium salt of a fatty acid having from 10 about 10 to about 22 carbon atoms. Calcium oxide is a particularly preferred catalyst. The amount that can be used is an effective amount which is any amount required to effect the conversion of a sterol or stanol to the corresponding ester. Typically, the amount will range from about 0.01% to 0.2% based on the total weight of the reaction mixture and will preferably be 15 in the range of about 0.02% to about 0.05%.

The processes according to the invention can be carried out at a temperature in the range of from about 190°C to about 210°C. The temperature for a particular reaction will depend upon a number of factors such as the nature of the catalyst, the equipment in which the reaction is 20 carried out and whether a sterol or stanol is esterified or transesterified. If a sterol is used in the process according to the invention, a temperature in the range of 190°C to about 210°C is optimum. Such a temperature will minimize the dehydration of the sterol. If a stanol is used in the process according to the invention, a temperature up to about 210°C is optimum.

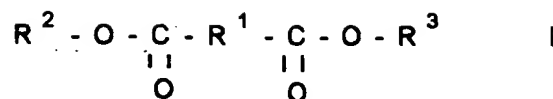
25 The transesterification process according to the invention can be carried out using any type of carboxylic acid ester. Such esters include simple esters such as lower alkyl esters which include, for example, methyl, ethyl, propyl, or butyl esters or higher alkyl esters such as pentyl, hexyl, heptyl and the like or triglycerides which are triglyceryl esters of C₆₋₂₂ fatty acids such as 30 conventional fats or oils. The transesterification conditions will vary according to the type of ester employed. If a glyceride is used, the temperature will be in the range of from about 210°C to about 250°C, preferably from about 220°C

to about 230°C. If an ester of a lower molecular weight alcohol is used such as a methyl or ethyl ester such that the alcohol formed will be readily removed under the reaction conditions as, opposed to the use of a triglyceride where the glycerin formed is not as readily removed, the temperature will be in the range of from about 100°C to about 130°C, preferably from about 110°C to about 120°C.

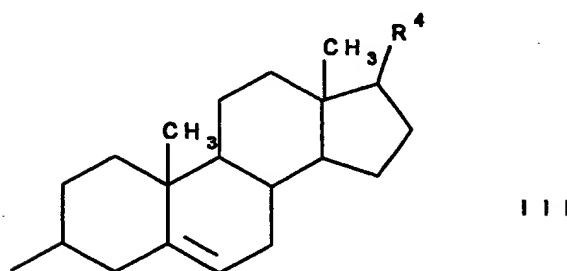
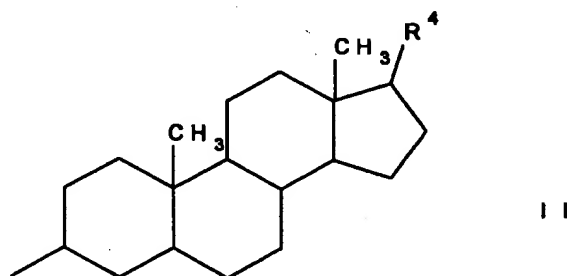
The direct esterification process according to the invention can be carried out by mixing the reactants in a batch reactor and heating the reactor contents to an appropriate temperature to remove the water of reaction. This may be accomplished at atmospheric pressure or below. Another method of carrying out the process according to the invention is to pass the reaction mixture through an evaporator such as a thin film evaporator or wiped film evaporator operating at a pressure of about 2-3 millibars and at a temperature of about 230°C while the reaction is taking place or after the reaction has been completed. It is preferable to operate the evaporator using an inert gas or vapor such as nitrogen or steam such that the inert gas or vapor contacts the thin film of reaction mixture in a counter-current fashion. The reaction mixture is passed through the evaporator one or more times in order to increase the surface to volume ratio to more efficiently remove the water of reaction thereby decreasing the time the reaction mixture spends at elevated reaction temperatures. One embodiment of the aforementioned method is a combination of a stirred tank reactor and an evaporator wherein the reactants are heated to reaction temperature and then repeatedly circulated through the evaporation means. An advantage of carrying out the process according to the invention on a commercial scale is that since no low molecular weight alcohol is produced as in, for example, transesterification of a methyl ester, there is no foaming in a reactor due to the evolution of the low molecular weight alcohol such as methanol. Therefore, the full working volume of the reactor can be utilized without an allowance for foam volume.

The process according to the invention is particularly useful for the preparation of dicarboxylic acid esters of sterols and/or stanols wherein the dicarboxylic acids are fully esterified or partially esterified. Such compounds

have the formula I

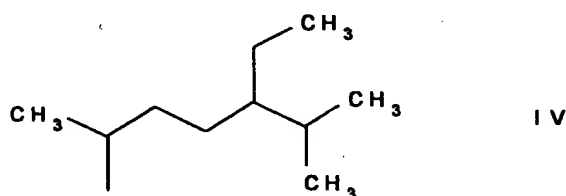


wherein R¹ is an aliphatic or aromatic moiety having from one to about 36 carbon atoms. Examples of possible values of R¹ include, but are not limited to, branched and unbranched alkylene and alkenylene radicals having from 2 to 18 carbon atoms; dimer acid residues which are cycloaliphatic moieties having 34 carbon atoms; aromatic radicals and each of R² and R³ is hydrogen, or a radical of the formula II or formula III



wherein R⁴ is an alkyl, substituted alkyl, alkenyl or substituted alkenyl group having from one to about 10 carbon atoms; each of R² or R³ is independently hydrogen with the proviso that only one of R² or R³ can be hydrogen. In the instances where only one of R² or R³ is hydrogen refer to the partial or half esters of the dicarboxylic acids. These compounds are useful as for reducing

serum cholesterol and LDL levels. Preferred compounds of the formula I include those wherein R^1 is an alkylene radical having from 2 to 18 carbon atoms with alkylene radicals having 7, 8, 10, and 11 carbons being especially preferred; each of R^2 and R^3 is a radical of the formula II wherein R^4 is an alkyl radical having from 2 to 10 carbon atoms. Preferred values of R^4 include a branched alkyl group having 10 carbon atoms. A most preferred R^4 is an alkyl group of the formula IV



Most preferred compounds of the formula I include the disitostanol ester of azelaic acid, the disitostanol ester of brassylic acid, the disitostanol ester of decanedioic acid, the disitostanol ester of dodecanedioic acid, the disitosterol ester of azelaic acid, the disitosterol ester of brassylic acid, the disitostanol ester of decanedioic acid and, the disitosterol ester of dodecanedioic acid, the sitostanol monoester of azelaic acid, the sitostanol monoester of brassylic acid, the sitostanol monoester of decanedioic acid, the sitostanol monoester of dodecanedioic acid, the sitosterol monoester of azelaic acid, the sitosterol monoester of brassylic acid, the sitostanol monoester of decanedioic acid and, the sitosterol monoester of dodecanedioic acid.

The following examples are meant to illustrate but not to limit the invention.

EXAMPLE 1

About 250 grams of sunflower fatty acid (acid value = 200.1) was added to a clean, dry vessel under nitrogen, heated to 130°C with agitation and nitrogen sparge. About 357 grams of mixed stanols (hydrogenated

GENEROL® 122N sterol) was added at a rate slow enough to avoid cooling while agitating with a nitrogen sparge. This required about one half hour. After the addition of the stanol, 0.34 grams of calcium hydroxide was added and the pressure was gradually decreased to 27 inches, while the
5 temperature was increased to 230°C. After six hours, the pressure was reduced to 40 mm Hg while maintaining the heat at 230°C for another six hours. The reaction mixture was cooled under vacuum and the vacuum broken with nitrogen. The acid value at this point was 7.4. A solution of 2.7 grams of tartaric acid in 20 ml water was added to the crude product at 80°C
10 with agitation and nitrogen sparge. The mixture was then heated to 110°C and 27 inches vacuum for a half hour to remove water. TONSIL® Optimum FF bleaching clay was then added under nitrogen, the mixture agitated for a half hour and filtered through a bed of CELITE® filter aid on a heated Buchner funnel. The batch lightened upon neutralization of the catalyst and
15 filtration.

ANALYSIS

Appearance: Clear yellow liquid which sets up to a wax

Color (Gardner): 5

Acid Value: 7.35

20 % Stanol: 4.4

Ppm Calcium: 1

EXAMPLE 2

About 250 grams of sunflower fatty acid (acid value = 200.1) was added to a clean, dry vessel under nitrogen, heated to 130°C with agitation
25 and nitrogen sparge. About 357 grams of mixed sterols (GENEROL® 122N sterol) was added at a rate slow enough to avoid cooling while agitating with a nitrogen sparge. This required about one half hour. After the addition of the stanol, 0.34 grams of calcium oxide was added and the pressure was gradually decreased to 27 inches, while the temperature was increased to
30 210°C. After six hours, the pressure was reduced to 40 mm Hg while

maintaining the heat at 230°C for another six hours. The reaction mixture was cooled under vacuum and the vacuum broken with nitrogen. The acid value at this point was 7.4. A solution of 2.7 grams of tartaric acid in 20 ml water was added to the crude product at 80°C with agitation and nitrogen sparge. The mixture was then heated to 110°C and 27 inches vacuum for a half hour to remove water. TONSIL® Optimum FF bleaching clay was then added under nitrogen, the mixture agitated for a half hour and filtered through a bed of CELITE® filter aid on a heated Buchner funnel. The batch lightened upon neutralization of the catalyst and filtration.

10

EXAMPLE 3

A dicarboxylic ester is made by reacting one mole of a sterol or stanol with a 1/2 mole of a dicarboxylic acid in the presence of calcium oxide at 210 degrees under reduced pressure according to the procedure of Examples 1 and 2 above.

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EXAMPLE 4

About 312 grams of sunflower fatty acid (acid value = 200.1) was added to a clean, dry vessel under nitrogen, heated to 120°C with agitation and nitrogen sparge. About 357 grams of GENEROL® 122N sterol was added at a rate slow enough to avoid cooling while agitating with a nitrogen sparge. This required about one half hour. After the addition of the GENEROL® 122N, 0.34 grams of calcium oxide was added and the pressure was gradually decreased to 30 mbar while the temperature was increased to 210°C. After six hours at 210°C and < 30 mbar, the reaction mixture was cooled under vacuum, and the acid value at this point was 22.2. A solution of 3.72 g tartaric acid in 23 g water was added to the crude product at 80°C with agitation and nitrogen sparge. The mixture was then heated to 90°C and 17 mbar for one hour. The vacuum was released with nitrogen, added 2 g of TONSIL® FF, 1.4 g of Clarcel DICB, evacuated to < 30 mbar and filtered at 90°C. The batch lightened upon neutralization of the catalyst and filtration. The crude product contained 4.7% unreacted sterol via GC analysis.

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What is claimed is:

1. A process for making a food additive comprising combining an edible solubilizing agent, an effective amount of a suitable antioxidant, an effective amount of a suitable dispersant and a sterol or stanol ester made by reacting
5 a sterol or a stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.
2. The process of claim 1 wherein the sterol is β -sitosterol.
- 10 3. The process of claim 1 wherein the sterol is β -sitostanol.
4. The process of claim 1 wherein the catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.
5. The process of claim 1 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.
- 15 6. A process which comprises reacting β -sitostanol with a carboxylic acid in the presence of an effective amount of calcium oxide.
7. The process of claim 6 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.
8. The process of claim 1 wherein the carboxylic acid is a mixture of long
20 chain carboxylic acids derived from sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame oil, safflower oil.
9. A process which comprises reacting β -sitosterol with a carboxylic acid in the presence of an effective amount of calcium oxide.

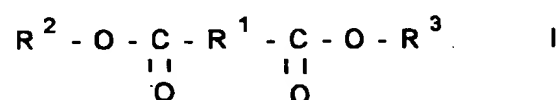
10. The process of claim 1 wherein the antioxidant is vitamin C, vitamin E, β -carotene, an extract of the bark of the maritime pine, *Pinus maritima*, or combinations thereof.
- 5 11. A food additive composition comprising an edible solubilizing agent, an effective amount of a suitable antioxidant and an effective amount of a suitable dispersant and a sterol or stanol ester made by reacting a sterol or a stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and
10 combinations thereof.
12. The composition of claim 11 wherein the sterol is β -sitosterol.
13. The composition of claim 11 wherein the stanol is β -sitostanol.
14. The composition of claim 11 wherein the catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.
- 15 15. The composition of claim 11 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.
16. The composition of claim 11 wherein the antioxidant is vitamin C, vitamin E, β -carotene, an extract of the bark of the maritime pine, *Pinus maritima*, or combinations thereof.
- 20 17. The composition of claim 11 wherein the carboxylic acid is a mixture of long chain carboxylic acids derived from sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame oil, safflower oil.
18. The composition of claim 17 wherein the mixture of long chain

carboxylic acids derived from sunflower oil.

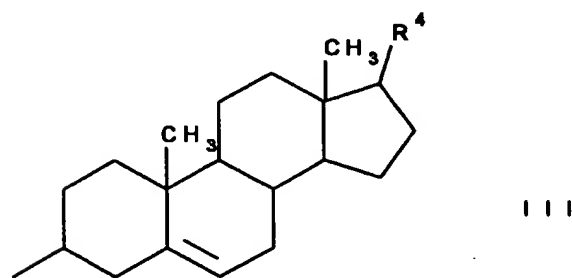
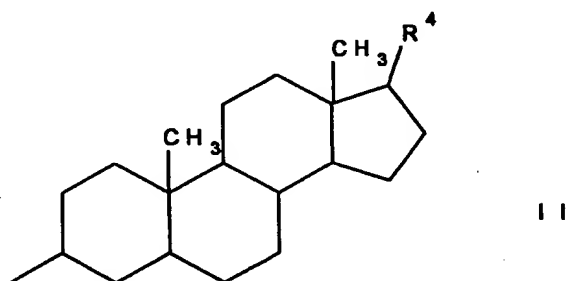
19. A process which comprises reacting β -sitosterol with a carboxylic acid in the presence of an effective amount of calcium oxide.
20. The composition of claim 11 wherein the antioxidant is vitamin C, vitamin E, β -carotene, an extract of the bark of the maritime pine, *Pinus maritima*, or combinations thereof.
21. A food additive made by the process comprising combining an edible solubilizing agent, an effective amount of a suitable antioxidant, an effective amount of a suitable dispersant and a sterol or stanol ester made by reacting a sterol or a stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.
22. The food additive of claim 21 wherein the sterol is β -sitosterol.
23. The food additive of claim 21 wherein the sterol is β -sitostanol.
24. The food additive of claim 21 wherein the catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.
25. The food additive of claim 21 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.
26. The food additive of claim 21 wherein the carboxylic acid is a mixture of long chain carboxylic acids derived from sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame oil, safflower oil.

27. The food additive of claim 21 wherein the antioxidant is vitamin C, vitamin E, β -carotene, an extract of the bark of the maritime pine, *Pinus maritima*, or combinations thereof.

28. A composition comprising an edible solubilizing agent, an effective amount of a suitable antioxidant, an effective amount of a suitable dispersant and a compound of the formula I



wherein R^1 is an aliphatic or aromatic moiety having from one to about 36 carbon atoms and each of R^2 and R^3 is independently hydrogen with the proviso that only one of R^2 or R^3 is hydrogen, or a radical of the formula II or formula III



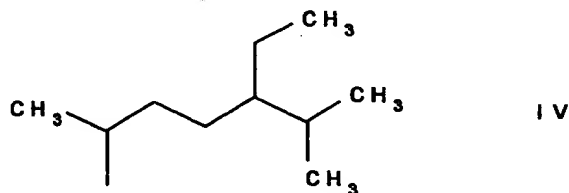
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wherein R^4 is an alkyl, substituted alkyl, alkenyl or substituted alkenyl group having from one to about 10 carbon atoms.

29. The composition of claim 28 wherein R^1 is an alkylene radical having from 2 to 18 carbon atoms; each of R^2 and R^3 is a radical of the formula II wherein R^4 is an alkyl radical having from 2 to 10 carbon atoms.

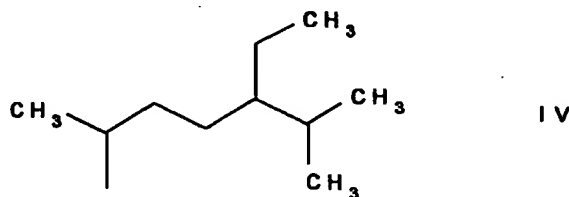
30. The composition of claim 28 wherein R^1 is an alkylene radical having 7 carbon atoms and wherein each of R^2 and R^3 is a radical of the formula II wherein R^4 is a branched alkyl group having 10 carbon atoms.

31. The composition of claim 30 wherein said branched alkyl group has the formula IV



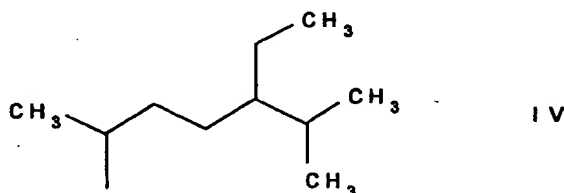
32. The composition of claim 28 wherein R^1 is an alkylene radical having 8 carbon atoms and wherein each of R^2 and R^3 is a radical of the formula II wherein R^4 is a branched alkyl group having 10 carbon atoms.

33. The composition of claim 32 wherein said branched alkyl group has the formula IV



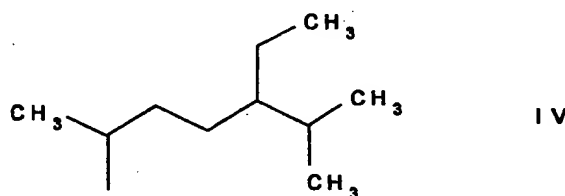
34. The composition of claim 28 wherein R¹ is an alkylene radical having 10 carbon atoms and wherein each of R² and R³ is a radical of the formula II wherein R⁴ is a branched alkyl group having 10 carbon atoms.

5 35. The composition of claim 34 wherein said branched alkyl group has the formula IV

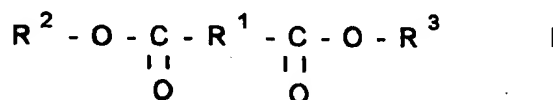


36. The composition of claim 28 wherein R¹ is an alkylene radical having 11 carbon atoms and wherein each of R² and R³ is a radical of the formula II wherein R⁴ is a branched alkyl group having 10 carbon atoms.

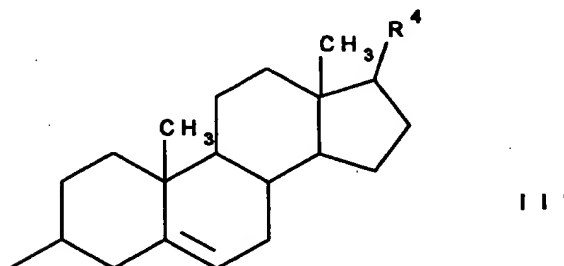
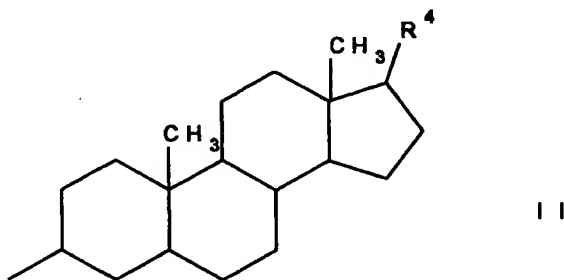
10 37. The composition of claim 36 wherein said branched alkyl group has the formula IV



38. A composition made by the process which comprises combining an edible solubilizing agent, an effective amount of a suitable antioxidant, an effective amount of a suitable dispersant and a compound of the formula I



wherein R^1 is an aliphatic or aromatic moiety having from one to about 36 carbon atoms and each of R^2 and R^3 is independently hydrogen with the proviso that only one of R^2 or R^3 is hydrogen, or a radical of the formula II or formula III

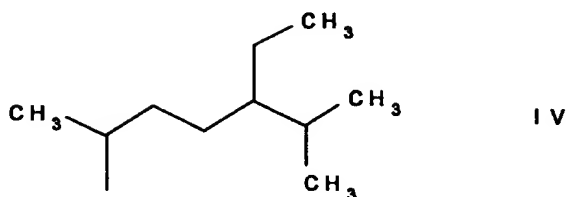


- 5 wherein R^4 is an alkyl, substituted alkyl, alkenyl or substituted alkenyl group having from one to about 10 carbon atoms.

39. The composition of claim 38 wherein R^1 is an alkylene radical having from 2 to 18 carbon atoms; each of R^2 and R^3 is a radical of the formula II wherein R^4 is an alkyl radical having from 2 to 10 carbon atoms.

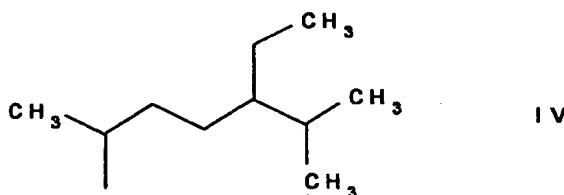
- 10 40. The composition of claim 38 wherein R^1 is an alkylene radical having 7 carbon atoms and wherein each of R^2 and R^3 is a radical of the formula II wherein R^4 is a branched alkyl group having 10 carbon atoms.

41. The composition of claim 40 wherein said branched alkyl group has the formula IV



42. The composition of claim 38 wherein R¹ is an alkylene radical having 8 carbon atoms and wherein each of R² and R³ is a radical of the formula II wherein R⁴ is a branched alkyl group having 10 carbon atoms.

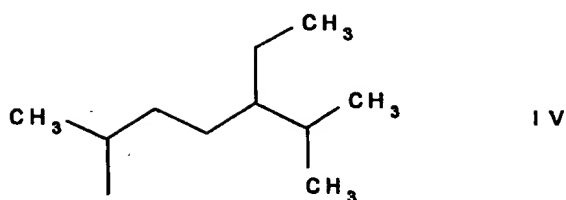
43. The composition of claim 42 wherein said branched alkyl group has the formula IV



44. The composition of claim 38 wherein R¹ is an alkylene radical having 10 carbon atoms and wherein each of R² and R³ is a radical of the formula II wherein R⁴ is a branched alkyl group having 10 carbon atoms.

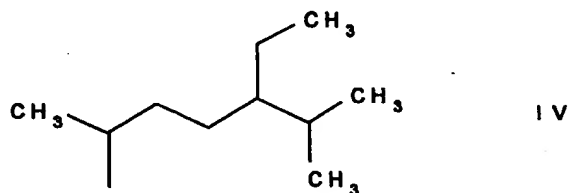
45. The composition of claim 44 wherein said branched alkyl group has the formula IV

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46. The composition of claim 38 wherein R^1 is an alkylene radical having 11 carbon atoms and wherein each of R^2 and R^3 is a radical of the formula II wherein R^4 is a branched alkyl group having 10 carbon atoms.

5 47. The composition of claim 46 wherein said branched alkyl group has the formula IV



10 48. A method of reducing the absorption of cholesterol into the bloodstream comprising orally introducing into the body an effective amount of a substance containing a β -sitostanol ester wherein the ester is made by reacting β -sitostanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

15 49. The method of claim 48 wherein the substance containing a β -sitostanol ester is comprised of an additive comprised of from about 70% to about 80% sunflower oil, rape seed oil or a combination thereof; from about 1% to about 2% vitamin E, an extract of the bark of the maritime pine, Pinus

maritima or a combination thereof; and from about 10% to about 25% of a β -sitostanol fatty acid ester prepared by the method according to the invention.

50. The method of claim 48 wherein an effective amount of the substance is from about 0.2 to about 2.0 grams per day.

5 51. The process of claim 48 wherein the catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

52. The process of claim 48 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

10 53. A process which comprises reacting a sterol, a stanol, or a combination thereof with a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

54. The process of claim 53 wherein said sterol is β -sitosterol.

15 55. The process of claim 53 wherein said stanol is β -sitostanol.

56. The process of claim 53 wherein said catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

57. The process of claim 53 wherein said carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

20 58. A process which comprises reacting β -sitostanol with a carboxylic acid in the presence of an effective amount of calcium oxide.

59. The process of claim 58 wherein said carboxylic acid is a carboxylic

acid having from about 2 to 22 carbon atoms.

60. The process of claim 59 wherein said carboxylic acid is a mixture of long chain carboxylic acids derived from sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame oil, safflower oil.

61. A process which comprises the steps of: (1) forming a reaction mixture comprised of a sterol, a stanol, or a combination thereof with a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium hydroxide, magnesium hydroxide and a combination in a reaction zone; (2) passing at least a portion of said reaction mixture through an evaporation zone to remove the water of reaction from said reaction mixture.

62. The process of claim 61 further comprising the step of returning the mixture from step (2) to said reaction zone.

63. The process of claim 61 wherein said catalyst is calcium oxide.

64. A process which comprises reacting a sterol, a stanol, or a combination thereof with an carboxylic acid ester in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

65. The process of claim 64 wherein said sterol is β -sitosterol.

66. The process of claim 64 wherein said stanol is β -sitostanol.

67. The process of claim 64 wherein said catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

68. The process of claim 64 wherein said carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

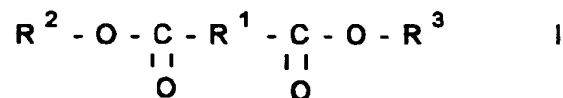
69. The process of claim 64 wherein said ester is a methyl ester of a C₆₋₂₂ fatty acid or a triglyceride.

5 70. A process which comprises reacting β -sitostanol with a carboxylic acid ester in the presence of an effective amount of calcium oxide.

71. A process which comprises the steps of: (1) forming a reaction mixture comprised of a sterol, a stanol, or a combination thereof with a carboxylic acid ester in the presence of an effective amount of a catalyst selected from the
10 group consisting of calcium hydroxide, magnesium hydroxide and a combination in a reaction zone; (2) passing at least a portion of said reaction mixture through an evaporation zone to remove the water of reaction from said reaction mixture.

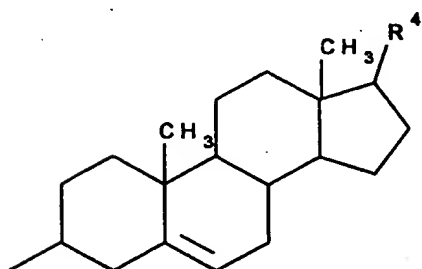
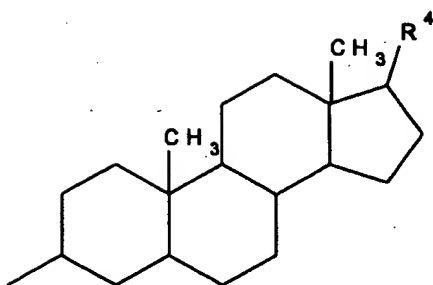
72. The process of claim 71 further comprising the step of returning the
15 mixture from step (2) to said reaction zone.

73. A compound of the formula I



wherein R¹ is an aliphatic or aromatic moiety having from one to about 36 carbon atoms and each of R² and R³ is independently hydrogen with the proviso that only one of R² or R³ is hydrogen, or a radical of the formula II or
20 formula III

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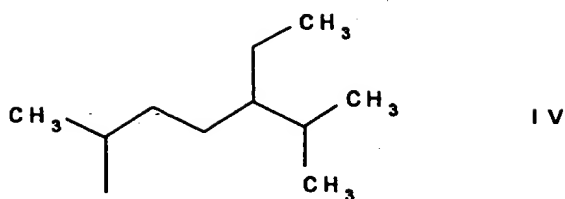
wherein R^4 is an alkyl, substituted alkyl, alkenyl or substituted alkenyl group having from one to about 10 carbon atoms.

74. The compound of claim 73 wherein R^1 is an alkylene radical having from 2 to 18 carbon atoms; each of R^2 and R^3 is a radical of the formula II wherein R^4 is an alkyl radical having from 2 to 10 carbon atoms.

75. The compound of claim 73 wherein R^1 is an alkylene radical having 7 carbon atoms and wherein each of R^2 and R^3 is a radical of the formula II wherein R^4 is a branched alkyl group having 10 carbon atoms.

76. The compound of claim 73 wherein said branched alkyl group has the formula IV

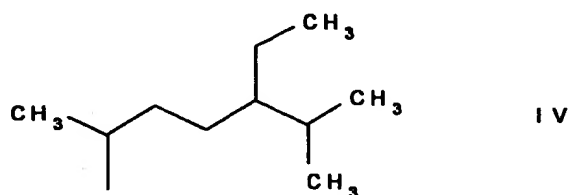
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77. The compound of claim 73 wherein R^1 is an alkylene radical having 8 carbon atoms and wherein each of R^2 and R^3 is a radical of the formula II wherein R^4 is a branched alkyl group having 10 carbon atoms.

78. The compound of claim 77 wherein said branched alkyl group has the formula IV

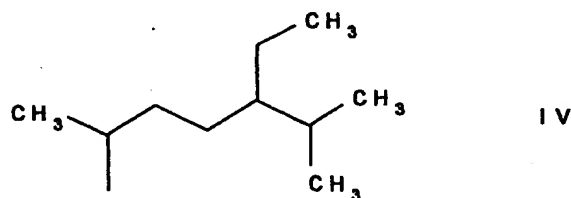
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79. The compound of claim 77 wherein R^1 is an alkylene radical having 10 carbon atoms and wherein each of R^2 and R^3 is a radical of the formula II wherein R^4 is a branched alkyl group having 10 carbon atoms.

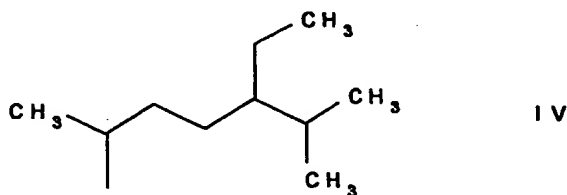
80. The compound of claim 77 wherein said branched alkyl group has the formula IV

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81. The compound of claim 73 wherein R^1 is an alkylene radical having 11 carbon atoms and wherein each of R^2 and R^3 is a radical of the formula II wherein R^4 is a branched alkyl group having 10 carbon atoms.

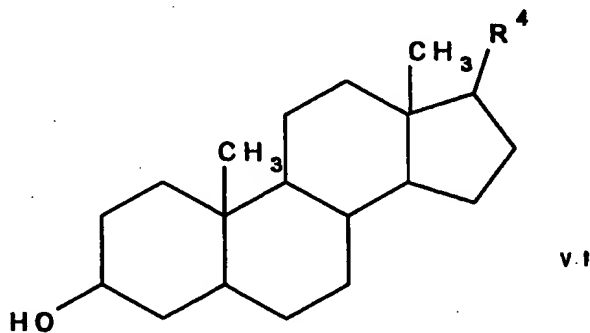
5 82. The compound of claim 81 wherein said branched alkyl group has the formula IV



83. A compound which is the product of the process which comprises reacting a sterol, a stanol, or a combination thereof with a dicarboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

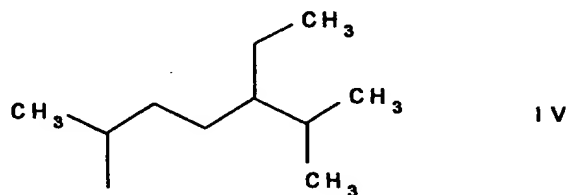
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84. The compound of claim 83 wherein said stanol is a compound of the formula VI

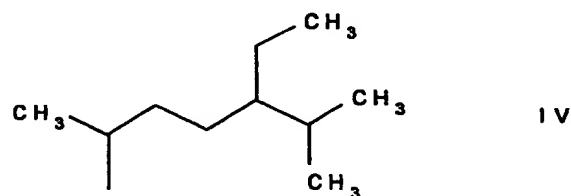


wherein R⁴ is an alkyl, substituted alkyl, alkenyl or substituted alkenyl group having from one to about 10 carbon atoms.

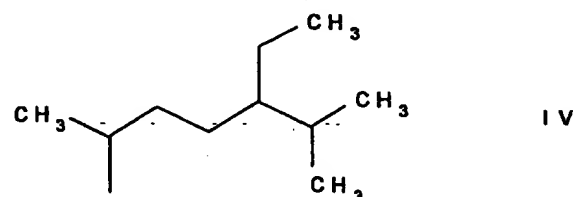
85. The compound of claim 84 wherein said dicarboxylic acid is azelaic acid and wherein said branched alkyl group of the formula IV



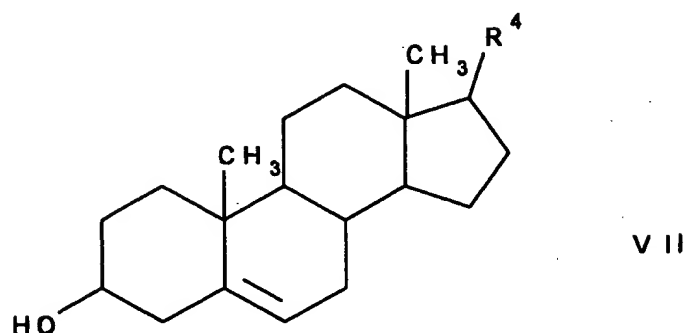
5 86. The compound of claim 84 wherein said dicarboxylic acid is dodecanedioic acid and wherein said branched alkyl group of the formula IV



87. The compound of claim 84 wherein said dicarboxylic acid is brassylic acid and wherein said branched alkyl group of the formula IV

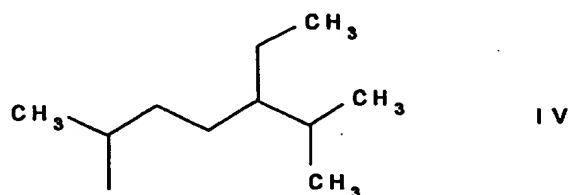


88. The compound of claim 83 wherein said sterol is a compound of the formula VII

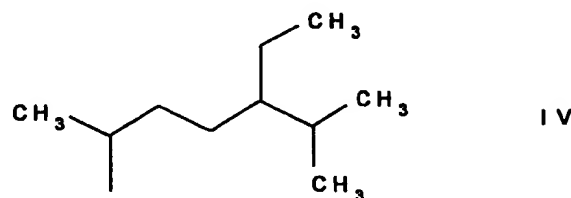


wherein R^4 is an alkyl, substituted alkyl, alkenyl or substituted alkenyl group having from one to about 10 carbon atoms.

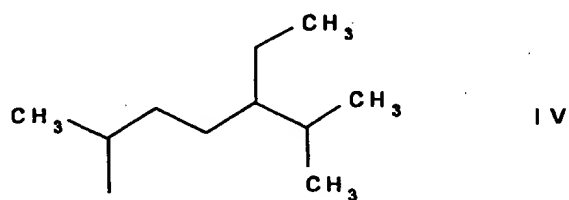
5 89. The compound of claim 88 wherein said dicarboxylic acid is azelaic acid and wherein said branched alkyl group of the formula IV



90. The compound of claim 88 wherein said dicarboxylic acid is dodecanedioic acid and wherein said branched alkyl group of the formula IV



91. The compound of claim 88 wherein said dicarboxylic acid is brassylic acid and wherein said branched alkyl group of the formula IV



92. The compound of claim 83 wherein said catalyst is calcium oxide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/26212

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A23D 7/00; A61K 35/78

US CL : 426/271, 601, 605; 536/5, 62; 514/783; 532/502; 424/195.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 426/271, 601, 605; 536/5, 62; 514/783; 532/502; 424/195.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,270,041 A (EUGSTER et al.) 14 Dec. 1993, see whole document, especially lines 42-50, column 13.	1, 3-8, 10, 11, 13-18, 20, 21, and 23-47
X	US 5,514,398 A (IMAI et al.) 07 May 1996, see lines 17-33, column 3, lines 13-56, column 4.	1, 3-8, 10, 11, 13-18, 20, 21, 23-27 and 48
Y	US 5,883,087 A (BERLINER et al.) 16 March 1999, see whole document.	11, 13-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

28 MARCH 1999

Date of mailing of the international search report

07 MAY 1999

Name and mailing address of the ISA/US
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/26212

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MIETTINEN, T. A. Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population, The new England Journal of Medicine, Nov. 16, 1995, Vol. 333, No. 20, pages 1308-1312, especially Table 3, page 1311.	1, 3-8, 10, 11, 13-18, 20, 21, 23-27 and 48

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US98/26212**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please see Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 3-8, 10, 11, 13-18, 20, 21, 23-27 and 48

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/26212

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, Claims 1, 3-8, 10, 11, 13-18, 20, 21, 23-27 and 48 are drawn to composition, process of making food additives, and method of use when the compound is b-sitostanol.

Group II, Claims 1, 2, 4, 5, 8, 9, 10, 11, 12, 14-22, 24-27 and 48 are drawn to process of making food additives, compositions and method of use when the compound is b-sitosterol.

Group III, Claims 28-36, 38-47 (compositions) drawn to compounds, composition of compound of Formula I, when R_1 is alkylene or alkenylene and one of the R_2 or R_3 is Hydrogen and the other is formula II.

Group IV, Claims 28, 38-47 are drawn to compounds, composition of the compound of Formula I, when R_1 is alkylene or alkenylene and one of the R_2 or R_3 is Hydrogen and the other is formula III.

Group V, Claims 38-47 are drawn to process of making sterols of Formula I, when R_1 is alkylene or alkenylene and one of the R_2 or R_3 is Hydrogen and the other is formula II.

Group VI, Claims 38-47 are drawn to process of making stanols of Formula I, when R_1 is alkylene or alkenylene and one of the R_2 or R_3 is Hydrogen and the other is formula III.

Group VI, Claims 49-52, are drawn to method of use of sterol.

Group VII, Claims 49-52, are drawn to method of use of stanol.

Group VIII, Claims 53, 55, 56-60, are drawn to process of making stanol.

Group IX, Claims 53, 54, 56-60, are drawn to process of making stanol.

Group X, Claims 61-65, 67-69, are drawn to process of making sterol.

Group XI, Claims 61-65, 66, 68 and 69, are drawn to process of making stanol.

Group XII, Claims 71 and 72 are drawn to process of making stanol.

Group XIII, Claims 71 and 72, are drawn to process of making sterol.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/26212

Group XIV, Claims 73-82 are drawn to compounds of Formula I, when R₁ is alkylene or alkenylene and one of the R₂ or R₃ is Hydrogen and the other is formula II.

Group XV, Claims 73-82 are drawn to compounds of Formula I, when R₁ is alkylene or alkenylene and one of the R₂ or R₃ is Hydrogen and the other is formula III.

Group XVI, Claims 83-87 are drawn to when the compounds are stanol of formula VI.

Group XVII, Claims 83, 88-92 are drawn to when the compounds are sterol of formula VII.

Group XVIII, Any other not included in Groups I-XVII. If applicant elect group XVIII further restriction may be required.

Note: The term alkyl polyglycosides are limited to examples on page 5, lines 1 and 2, as substituent R₁ in formula V (page 4, line 15 cannot be searched. (See definition of R₁).

The inventions listed as Groups I-XVIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Compounds, corresponding compositions, process of making and methods of use that are of the same scope are considered to form a single inventive concept as required by PCT Rule 13.1 CFR 1.475(d). The groups as outlined above are not so linked as to form a single inventive concept as they are either drawn to dissimilar compounds of varying cores and functional moieties, different processes of making the compounds, or food additives, which are separately classified, require separate literature searches, and are not art recognized equivalents.